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Review

Exposure to electromagnetic fields (non-ionizing radiation) and its relationship with childhood leukemia: A systematic review

I. Calvente [a,b], M.F. Fernandez [a,b], J. Villalba [b], N. Olea [a,b], M.I. Nuñez [b,*]

[a] Laboratory of Medical Investigations, San Cecilio University Hospital, CIBER de Epidemiología y Salud Pública (CIBERESP), Spain
[b] Department of Radiology, University of Granada, Granada, Spain

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ABSTRACT

Childhood exposure to physical contamination, including non-ionizing radiation, has been implicated in numerous diseases, raising concerns about the widespread and increasing sources of exposure to this type of radiation. The primary objective of this review was to analyze the current state of knowledge on the association between environmental exposure to non-ionizing radiation and the risk of childhood leukemia. Scientific publications between 1979 and 2008 that include examination of this association have been reviewed using the MEDLINE/PubMed database. Studies to date have not convincingly confirmed or ruled out an association between non-ionizing radiation and the risk of childhood leukemia. Discrepancies among the conclusions of the studies may also be influenced by confounding factors, selection bias, and misclassification. Childhood defects can result from genetic or epigenetic damage and from effects on the embryo or fetus, which may both be related to environmental exposure of the parent before conception or during the pregnancy. It is therefore critical for researchers to define *a priori* the type and "window" of exposure to be assessed. Methodological problems to be solved include the proper diagnostic classification of individuals and the estimated exposure to non-ionizing radiation, which may act through various mechanisms of action. There appears to be an urgent need to reconsider exposure limits for low frequency and static magnetic fields, based on combined experimental and epidemiological research into the relationship between exposure to non-ionizing radiation and adverse human health effects.

Contents

1. Introduction

Humans have been constantly exposed to electromagnetic radiation, including sunlight, cosmic rays, and terrestrial radiations. However, a substantial increase in exposure, especially to low-frequency electromagnetic radiation (EMR), started in the early

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; EMR, electromagnetic radiation; ELF-EMR, extremely low-frequency electromagnetic radiation; ICNIRP, International Council of Non-Ionizing Radiation Protection; NIR, non-ionizing radiation; LF-EMR, low-frequency electromagnetic radiation; RF, radio frequencies.

* Corresponding author. Department of Radiology. University of Granada, 18071-Granada, Spain. Tel.: +34 958 24 2077; fax: +34 958 249953.
E-mail address: isabeln@ugr.es (M.I. Nuñez).

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20th century with the generation of artificial electromagnetic fields and continued with the development of power stations, radio, radar, television, computers, mobile phones, microwave ovens, and numerous devices used in medicine and industry. These technological advances have aroused concerns about the potential health risks associated with unprecedented levels of EMR exposure.

The amount of energy deposited by EMR and the form of its absorption is determined by the frequency and type of incident radiation and by the nature of the tissue that absorbs it. According to its effects on the organism, EMR can be divided between ionizing radiation (including high-frequency radiation such as gamma rays and X-rays) and non-ionizing radiation (NIR; low to very low frequency). Ionizing radiation causes biological effects by directly or indirectly damaging the DNA molecule; the effects of this type of radiation are not addressed in the present review.

Exposure to the multiple sources of NIR (Table 1), including residential exposure to high-voltage power lines, transformers, and domestic electrical installations, varies in duration and according to the distance from the source. Exposure is usually to low-frequency (LF-EMR) or extremely low-frequency (ELF-EMR) radiation and is continuous and rising among populations in the industrialized world. Besides LF-EMR and ELF-EMR radiation, individuals are increasingly exposed to radio frequencies (RF) from television (TV) towers, radio stations, mobile phone/wi-fi systems, and personal computers. Table 1 summarizes the different types, frequency ranges, and sources of NIR. Nevertheless, the average magnetic flux density is generally considered to be below the maximum exposure limits established by different organizations such as the International Council of Non-Ionizing Radiation Protection (ICNIRP) or the Spanish Experts' Committee of Electromagnetic Fields and Public Health in our setting (2001, 2003).

In 1998, guidelines on reference values, exposure limits, and restrictions were issued by the ICNIRP and other with the aim of protecting citizens against the possible harmful effects of acute exposure to this type of radiation (Table 2). The exposure limit for the general public is currently 50 Hz at 100 μT and higher frequencies (Table 2) (ICNIRP, 1998). These limits had previously been established by the IEEE (Institute of Electric and Electronics Engineers, Inc, 1992), also based on protection from immediate short-term effects. Although there is experimental evidence of biological responses at non-thermal NIR levels, it is not considered sufficiently robust or relevant to establish their potential impact on health (Kundi et al., 2009).

Among the few studies on magnetic flux density (magnetic flux density mapping), some show that the established limits were exceeded in a number of areas of Eastern Europe and North America (Kheifest et al., 2006; Maslanyj et al., 2007; Straume et al., 2008). In Spain, exposure to EMR has been measured in schools in the cities of Oviedo and Barcelona and in the region of Extremadura (Tardón et al., 2002; Paniagua et al., 2002), and magnetic flux density has been mapped in Extremadura (Paniagua et al., 2004).

Children are considered more vulnerable than adults to environmental exposure and deserve special research attention (Fernández et al., 2007; Ramón et al., 2005). Childhood exposure to physical contamination, including NIR, has been implicated in numerous diseases, raising concerns about their widespread and increasing use of mobile phones and other sources of NIR. The first authors to report a possible link between leukemia and environmental factors were Ager et al. (1965). Since then, a significant increase in the incidence of childhood leukemia has been reported in Europe and the United States, identifying clusters of cases associated with potential environmental etiological components (Draper et al., 2005; McNally and Parker, 2006). A study in 2001 reported that the incidence of leukemia among 2 to 4-year-olds was higher in industrialized countries than in developing countries, especially for the common subtype of acute lymphoblastic leukemia (ALL) (Milham and Ossiander, 2001). They investigated the advance of electrification between 1920 and 1960 and detected a peak in childhood leukemia incidence rates in 1930 in all states that had introduced electricity in >75% of residences. By 1950, an elevated incidence was recorded in all states but was more pronounced in those with a higher percentage of households connected to mains electricity. According to the authors, the association of leukemia with urbanization, modernization, and industrialization may be explained by the increase in electrification.

The annual incidence of childhood leukemia was estimated to be 4/100,000 by the WHO and 5/100,000 by the ICNIRP, in 2003. In our setting, 107 new cases (under 15 years old) were recorded in the Cancer Registry of Granada province (Spain) between 1985 and 2004, representing a mean annual incidence of 3.25/100,000 children, lower than in any other Spanish cancer registry. Nevertheless, according to the estimated cumulative rate (0.5‰) and if this trend continues, 1 out of every 2000 children living in Granada will develop leukemia before the age of 15 years (WHO: www.who.int/emf).

The primary objective of this review was to analyze the current state of knowledge on the association between environmental exposure to NIR and the risk of childhood leukemia.

Table 1
Frequencies and sources of non-ionizing radiation.

Frequency	Type of radiation	Sources
0 Hz–300 kHz	Low frequency to extremely low frequency (LF–ELF) electromagnetic radiation	Electrical fields of devices, conventional electrical network, video monitors, sections of AM radio
3 kHz–300 MHz	Radio frequencies (RF)	Sections of AM radio, FM radio, medical short-wave, nuclear magnetic resonance (NMR)
300 MHz–300 GHz	Microwave (MW)	Domestic microwave devices, mobile telephones, microwave for medical physical therapy, radar and other microwave communications
300 GHz–780 nm	Infrared (IR)	Solar light, heat and laser therapy devices
780 nm–400 nm	Visible light	Solar light, phototherapy, laser
400 nm–100 nm	Ultraviolet (UV)	Solar light, fluorescent tubes, food/air sterilization, radiotherapy, etc.

Hz: Hertz (kHz: kilohertz = 10^3 Hz; MHz: Megahertz s = 10^6 Hz; GHz: Gigahertz = 10^9 Hz). Ultraviolet (UV) within the range 280–185 nm is considered as ionizing radiation.

2. Mechanisms

Our working hypothesis was that NIR may be an environmental risk factor for developing childhood leukemia. The greatest obstacle to

Table 2
Protection limits for exposure to electrical, magnetic, and electromagnetic fields.

Frequency range	Field intensity E (V/m)	Field B (μT)	Power density (W/m^2)
0–1 Hz	–	4×10^4	–
1–8 Hz	10,000	$4\times10^4/f^2$	–
8–25 Hz	10,000	$5000/f$	–
0.025–0.8 kHz	$250/f$	$5/f$	–
0.8–3 kHz	$250/f$	6.25	–
3–150 kHz	87	6.25	–
0.15–1 MHz	87	$0.92/f$	–
1–10 MHz	$87/f^{1/2}$	$0.92/f$	–
10–400 MHz	28	0.09	2
400–2000 MHz	$1.375\times f^{1/2}$	$0.0046\times f^{1/2}$	$f/200$
2–300 GHz	61	0.2	10

f: frequencies as indicated in the column of frequency range.

testing this hypothesis is the absence of a consensus on the effects of LF-EMR or ELF-EMR on the organism at organ, tissue, cell, or molecular level (Ruiz-Gómez et al., 2009).

Koifman (1993) suggested that EMR might be carcinogenic, and this proposition was subsequently supported by the findings of the "UK Childhood Cancer Study Investigators" (UKCCS, 1999). However, the International Agency for Research on Cancer (IARC) only began to consider LF and ELF electromagnetic fields as possible carcinogens (category 2B) after publication of the pooled analysis by Ahlbom et al. (2000) and Greenland et al. (2000). No classification of RF electromagnetic fields has been proposed (Schüz and Ahlbom, 2008).

Research has especially focused on the extremely low frequencies used in electrical power lines (50–60 Hz) (Carrubba and Marino, 2008; Coulton et al., 2004; Girgert et al., 2005; IARC and Working Group, 2002), and on radiofrequencies (RF: 3 kHz to 300 MHz) and microwaves (MW: 300 MHz to 3 GHz) typically used for cell phone transmissions (Valentini et al., 2007). The thermal effects of EMR *via* direct energy transfer are well established, while possible non-thermal effects are controversial (Carrubba and Marino, 2008; Coulton et al., 2004; de Pomerai et al., 2003; del Vecchio et al., 2009; Diem et al., 2005; Girgert et al., 2005). In fact, microwaves have been reported to exert non-thermal effects in biological systems, at least partially arising from alterations in the conformation of cellular proteins (de Pomerai et al., 2003).

It has also been suggested that ELF-EMR influences proliferation and DNA damage in both normal and tumor cells through the action of free radical species, with no significant temperature difference between culture media of exposed and unexposed cells (Wolf et al., 2005). Other studies revealed an increase in DNA single-strand breaks in cells of rats exposed to 2.45 GHz (Paulraj and Behari, 2006). However, it was also reported that oxidative DNA damage does not significantly contribute to the DNA fragmentation observed in human fibroblasts after ELF-EMR exposure (Focke et al., 2010). It was recently demonstrated that the DNA molecule can be adversely affected by intermittent exposure to ELF-EMR, which may explain the relationship between LF-EMR and childhood leukemia and would support the classification of EMR as a potential genotoxin (Ivancsits et al., 2002). In this context, Binhi (2008) reported that magnetic nanoparticles found in some organisms played a role in increasing the concentration of free radicals within cells, which may explain the genotoxic action exerted by LF-EMR on the DNA molecule of hematopoietic stem cells.

There have been recent reports of other types of EMR exposure, especially through contact currents or voltages, e.g., from the voltage between water pipes and earth. Contact currents can also result from induction caused by magnetic fields from nearby heavily loaded power lines. This form of exposure is more likely in residences with high magnetic fields, in which contact current from metallic fixtures during the bathing of children may lead to elevated bone-marrow doses of induced currents (Kavet and Zaffanella, 2002; Brain et al., 2003). Unfortunately, there are few data on the role of contact voltages, and further research is required in this area.

Various *in vitro* studies and animal experiments found that simultaneous exposure to ELF radiation enhanced the effects of physical or chemical carcinogens, showing positive associations with a non-linear dose–response curve for energy fields between 1 and 3 mT (Juutilainen et al., 2006).

In considering the relationship with childhood leukemia, the timing of exposure is an important issue, as is the history of exposure, including occupational exposure of the parents of children, especially of the mothers during pregnancy. Some authors have linked exposure to NIR with the risk of abortion or a moderate increase in the risk of ALL (Lee et al., 2002; Li et al., 2002; Infante-Rivard and Deadman, 2003). There have also been reports of overexposed fetuses in women receiving EMR doses within the established limits (Wu et al., 2007; Cech et al., 2007; Leitgeb and Cech, 2008).

3. Methods

We reviewed the scientific publications between 1979 and 2008 that include examination of the association between human exposure to NIR (LF-EMR, ELF-ERM, and/or RF) and childhood leukemia. The MEDLINE/PubMed database was first searched for papers written in English or Spanish, using the key words electromagnetic fields and childhood leukemia. References cited in these papers were also examined for any additional publications. Studies were then selected according to the following criteria: 1) the type of design and the study population are reported; 2) the type and timing of exposure are defined *a priori*, and 3) the statistical methods are described.

Issues of major interest were the methods (direct or indirect) used to measure exposure and data on the variables influencing the exposure of parents. Direct assessments of EMR exposure included spot measurements of the strength of electromagnetic fields (magnetic flux density) at 24 and 48 h and at 1 week.

4. Results

Selected studies were classified according to the type of NIR (LF-EMR, ELF-ERM or RF) as summarized below.

4.1. Non-ionizing radiation: low and extremely low-frequency electromagnetic fields

Table 3 lists studies on the association between LF/ELF NIR and childhood leukemia. They are divided between two time periods: 1979–2000 and 2001–2008, because the meta-analyses by Ahlbom et al. (2000) and by Greenland et al. (2000) represented a turning point in exposure assessment and results.

4.1.1. First period (1979–2000)

Before 2000, exposure to ELF radiation was estimated according to the distance from normal-to-high-voltage overhead power lines, using the wire code method. This method offers an indirect measurement of residential exposure to magnetic fields produced by electrical currents as a function of the distance from the residence to the electric power line, also taking into account the characteristics (e.g., wire-size) and location of the line.

We highlight the epidemiological study by Wertheimer and Leeper (1979) with a case–control design. It included patients with childhood leukemia diagnosed between 1976 and 1977 and living in Colorado (USA) and compared them with controls from 1950 to 1973. Children highly exposed to ELF radiation were found to have a two-fold higher risk of developing leukemia versus children with lower exposure (OR 2.28; 95% CI 1.34–3.91). This study was the first to propose and use the wire code approach, which was later considered to introduce a bias that invalidated results to some degree (Jones et al., 1993; Savitz and Poole, 2001; Schüz, 2007).

Greenland et al. (2000) analyzed 15 available studies and described a higher overall risk of leukemia with an OR of 1.65 (95% CI 1.15–2.36) in children exposed to magnetic fields above 0.3 μT in comparison to children exposed to fields <0.1 μT. The pooled analysis by Ahlbom et al. (2000) considered the results of 9 studies, involving a total of 3203 children with leukemia and ten thousand controls, and calculated a higher risk (RR 2.0; 95% CI 1.27–3.13) for children exposed to ≥0.4 μT radiation versus those exposed to <0.1 μT. Therefore, both pooled analyses described a similar increase in risk with higher levels of magnetic field.

4.1.2. Second period (2001–2008)

2001 saw the first publication of studies using a direct method to estimate exposure to EMR. It is based on spot measurements in rooms, especially bedrooms, determining mean exposure values for 24 h,

Table 3
Childhood leukemia epidemiologic studies: low and extremely low-frequency electromagnetic fields.

Authors	Country, study period, design	Exposure assessment	Exposure category	Outcome [95% CI]
Wertheimer and Leeper (1979)	USA (Colorado) 1950–1973 Case–control: 344 cancer deaths and controls from birth registry	Wire codes	LCC[a] (birth address) HCC	 OR: 2.28 [1.34–3.91]
Ahlbom et al. (2000)	Pooled analyses of 9 studies	24/48-hour magnetic field measurements or calculated magnetic fields	<0.1 μT 0.1–0.2 μT 0.2–0.4 μT ≥0.4 μT	 RR: 1.08 [0.89–1.31] RR: 1.11 [0.84–1.47] RR: 2.00 [1.27–3.13]
Greenland et al. (2000)	Meta-analyses with 15 studies	Wire code, 24/48-hour magnetic field measurements or calculated magnetic fields	≤0.1 μT 0.1–0.2 μT 0.2–0.3 μT >0.3 μT	 OR: 1.00 [0.81–1.22] OR: 1.13 [0.92–1.39] OR: 1.65 [1.15–2.36]
Feychting et al. (2000)	Sweden Children born between 1976–1977, and 1981–1982 Cohort of 235,635 children	Parental occupational exposure before conception	Father occupational exposure ≥ 0.3 μT Mother occupational exposure ≥ 0.3 μT Parental occupational exposure ≥ 0.3 μT	RR: 2.0 [1.1–3.5] RR: 1.2 [0.5–2.4] RR: 4.7 [1.2–18.2]
Schüz et al. (2001)	West Germany 1993(90)–1997(94) Case–control: 514 cases from cancer registry and 1301 controls from population registry	24-h measurements in child's bedroom, living room and perimeter measurements	<0.1 μT (MD 24 h)[a] 0.1–0.2 μT 0.2–0.4 μT ≥0.4 μT <0.1 μT (MD night-time)[a] 0.1–0.2 μT 0.2–0.4 μT ≥0.4 μT	 OR: 1.15 [0.73–1.81] OR: 1.16 [0.43–3.11] OR: 5.81 [0.78–43.2] OR: 1.42 [0.90–2.23] OR: 2.53 [0.86–7.46] OR: 5.53 [1.15–26.6]
Li et al. (2002)	USA (San Francisco) Prospective cohort of pregnant women: 969 cases	24-hour personal exposure and miscarriage	<1.6 μT ≥1.6 μT ≥1.6 μT (miscarriages — 10 weeks of gestation)	RR: 1.80 [1.20–2.07] RR: 3.1 [1.3–7.7]
Infante-Rivard and Deadman (2003)	Canada (Québec) 1980–1993 Case (ALL)–control	Cumulative maternal occupational exposure throughout pregnancy Three measurements: cumulative, average and maximum levels	≥0.4 μT Only working women All studied women	 OR: 2.2 [1.2–4.2][b] OR: 2.3 [1.3–4.0][b] OR: 2.3 [1.2–4.3][c] OR: 2.3 [1.3–4.0][c]
Draper et al. (2005)	England and Wales 1962–1995 Case–control: 29,081 cases and 29,081 controls from registries	Distance of residence to the nearest overhead power line	≥600 m (from power line)[a] 200–600 m <200 m	 RR: 1.22 [1.01–1.47] RR: 1.68 [1.12–2.52]
Kabuto et al. (2006)	Japan (metropolitan areas) 1999–2001 Case–control: 321 cases from several registries and 634 controls from residential registry	Measurement of 7-day measurements in child's bedroom, Spot measurements inside and outside the house	(ALL + AML) <0.1 μT (1 week TWA)[a] 0.1–0.2 μT 0.2–0.4 μT ≥0.4 μT <0.1 μT (1 week night-time)[a] 0.1–0.2 μT 0.2–0.4 μT ≥0.4 μT (ALL) <0.1 μT (1 week TWA)[a] 0.1–0.2 μT 0.2–0.4 μT ≥0.4 μT	 OR: 0.93 [0.51–1.71] OR: 1.08 [0.51–2.31] OR: 2.77 [0.80–9.57] OR: 0.97 [0.52–1.79] OR: 1.08 [0.47–2.47] OR: 2.87 [0.84–9.88] OR: 0.87 [0.45–1.69] OR: 1.03 [0.43–2.50] OR: 4.67 [1.15–19.0]
Feizi and Arabi (2007)	Iran Case–control: 60 cases and 59 controls	Distance of residence to high-voltage overhead power lines (≤500 m) Intensities of magnetic fields calculated by mean intensity of electrical current and other line characteristics	>0.45 μT 0.6 μT 0.35 μT	 OR: 8.67 [1.74–58.40] OR: 3.60 [1.11–12.39]
Mejia-Arangure et al. (2007)	Mexico (Mexico-City) 1995–2003 Case–control Children with Down's syndrome and acute leukemia	Spot measurements at front door; wire coding.	<0.1 μT (spot)[a] 0.1–0.4 μT 0.4–0.6 μT ≥0.6 μT Low according to Kaune-Savitz[a] Medium High	 OR: 0.94 [0.37–2.4] OR: 0.88 [0.15–5.1] OR: 3.70[1.05–13] OR: 5.8 [0.92–37] OR: 4.1 [0.66–25]

AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, HCC: high-current code, LCC: low-current code, MD: median, OR: odds-ratio, RR: relative risk, TWA: time-weighted average.

[a] Reference category.

[b] Adjusted (child age and sex).

[c] Adjusted: child age and sex, and maternal age.

48 h, and 1 week, while also considering the distance from high-voltage power lines. Account also began to be taken of maternal exposure during pregnancy and the occupational exposure of the parents. However, these improved measurement methods yielded similar outcomes and conclusions to those obtained in the first period (1979–2000).

Schüz et al. (2001) and Kabuto et al. (2006) conducted studies of exposure to NIR for 24 h and one week, respectively, using spot measurements of magnetic fields. No statistically significant associations with childhood leukemia were obtained. However, when exposure exceeded 0.4μT, the risk was estimated to be five-fold higher (OR 5.81; 95% CI 0.78–43.2) by Schüz et al. (2001) and more than two-fold higher (OR 2.77; 95% CI 0.80–9.57) by Kabuto et al. (2006), using 0.1 μT as reference category. Kabuto et al. also found a statistically significant risk (OR 4.7; 95% CI 1.15–19) for ALL.

One of the largest investigations into magnetic fields and childhood cancer was conducted by Draper et al. (2005) in England and Wales. In their epidemiological case–control study, the distance from the residence to high-voltage power lines was related to the relative risk of childhood leukemia, finding a significant risk for distances of 200–600 m (RR 1.22; 95% CI 1.01–1.47) and for distances less than 200 m (RR 1.68; 95% CI 1.12–2.52). Feizi and Arabi used the same approach in a residential area in northwest Iran, comparing between residences less and more than 500 m from high-voltage power lines (>4.5 μT) and obtaining an OR of 3.6 for the former (95% CI 1.11–12.39) (Feizi and Arabi, 2007). The authors concluded that the presence of high-voltage overhead power lines within 500 m of residential areas should be considered a risk factor for acute childhood leukemia. Mejia-Arangure et al. (2007) examined the effect of exposure to EMR in children with Down's syndrome and diagnosed with acute leukemia. They found a higher risk of leukemia (OR 3.7; 95% CI 1.05–13) for magnetic fields ≥ 0.6 μT.

Li et al. (2002) studied 969 cases of childhood leukemia in San Francisco, where they collected information on reproductive health. They studied women at ≤10 weeks of gestation and found no risk of miscarriage in those exposed to <1.6 μT but a high risk (RR 1.8; 95% CI 1.2–2.07) in those exposed to >1.6 μT. The association was stronger for women with a history of previous miscarriage or sub-fertility (RR 3.1; 95% CI 1.3–7.7).

Infante-Rivard and Deadman (2003) investigated the association between childhood leukemia and cumulative exposure to NIR during pregnancy in an epidemiological case–control study of 491 children (0–9 years) diagnosed with leukemia in Quebec between 1980 and 1993. Estimation of maternal exposure during pregnancy took account of: a) the cumulative exposure in μT-days, b) mean exposure, and c) maximum exposure. The results suggest that children of mothers exposed to electromagnetic fields ≥0.4 μT during pregnancy had an increased risk of leukemia (OR 2.2; 95% CI 1.2–4.2). Results were similar (OR 2.3; 95% CI 1.2–4.3) when potential confounding variables were included in the model (age and sex of children and age of mothers). Other studies have also reported an association between residential exposure to >0.4 μT NIR and childhood leukemia (Ahlbom et al., 2000; Feychting et al., 2000).

A cohort study conducted in Sweden by Feychting et al. (2000) showed an increased risk of leukemia in 10-year-old children whose parents had been exposed to ≥0.3 μT (RR 4.7; 95% CI 1.2–18.2), although this increase only reached significance in the boys (RR 2.2; 95% CI 1.0–4.5). Occupational exposure studies have in general suggested that children of mothers exposed during pregnancy to high levels of electromagnetic fields (≥0.4 μT) have a moderately increased risk of ALL (Feychting et al., 2000; Infante-Rivard and Deadman, 2003; Pearce et al., 2007).

No study of this type has yet been carried out in Spain. However, exposure to ELF-EMR in Spanish schools was assessed by Tardón et al. (2002) in the cities of Oviedo and Barcelona and by Paniagua et al. (2002) in the region of Extremadura. Both groups measured 24-h exposure levels (in classrooms, playground, etc.) and determined the distance from power lines. Mean exposure levels were similar in both cities (0.016 μT for Barcelona and 0.015 μT for Oviedo), with higher maximum exposure levels in Barcelona (0.057 μT) than in Oviedo (0.017 μT). Values never exceeded 0.3 μT in Oviedo but were much higher in three sites in Barcelona (0.62 μT, 0.49 μT, and 0.43 μT). With regard to sources of exposure, no transmission lines were located within the study area in four of the schools selected, whereas lines ran along the walls of classrooms in two other schools and were underground (at depth of 50 cm) in others. Paniagua et al. (2002) found generally low values in classrooms, offices, and leisure areas, but reported a mean value of 1.17 μT and maximum value of 37 μT in laboratories, which may be attributable to the presence of computers. Similar findings were described by Tardón et al. (2002). EMR levels found in the laboratories were similar to values estimated for professionally exposed workers (Merchant et al., 1994). These authors did not measure the daily total exposure and were therefore unable to estimate the proportion of exposure received by children during school hours. The authors concluded that proximity to power lines did not appear to be the main source of exposure to EMR and that the distribution of power transmission lines, underground cables, and other sources (e.g., transformers and electrical equipment) in the school may have significantly contributed to the children's exposure.

4.2. Non-ionizing radiation: radio frequency electromagnetic fields

Very few publications have investigated the effects on human health of exposure to NIR in the range of radio frequencies and microwaves, and most of these epidemiological studies had an ecological design, comparing leukemia incidence rates in different populations using aggregate data on exposure and disease, not individual data (Table 4).

In 2002, Michelozzi et al. analyzed the incidence of leukemia in the Vatican (Rome, Italy) between 1987 and 1999 and its relation to the Radio Vatican transmitter (Michelozzi et al., 2002). According to the 1991 census, 49,656 people lived within 10 km of the transmitter. The risk of childhood leukemia was higher for children living within 6 km (standardized incidence rate, SMR 2.2; 95% CI 1.0–4.1), observing a significant decline in risk with increasing distance ($p = 0.036$).The authors also reported an association between survival and the distance from the transmitter. However, the results of this study were limited by the small number of cases included ($n = 8$) and the absence of other exposure data.

Hocking and Gordon (2003) studied the incidence of childhood leukemia as a function of the distance from TV transmitters, finding an increased risk of leukemia in children living within a radius of less than 4 km compared with those living in a radius of 4 to 12 km. The mortality rate ratio between the inner and outer ring was 2.1 (95% CI 1.1–4.0), very similar to the findings reported by Michelozzi.

A case–control study in South Korea (Ha et al., 2007) examined exposure to amplitude modulated (AM) radio frequency from 31 towers and 49 antennas, transmitting with a power ≥20 kW and operating 24 h/day. The study included 1928 cases of leukemia diagnosed between 1993 and 1999 and 3082 controls. The estimated cancer risk was adjusted for socioeconomic status, area of residence, and population density. The risk of leukemia was higher in communities with low population density or lower economic status, but the differences were not statistically significant. The risk was significantly greater for children living within 2 km of AM source in comparison to those residing at distances >20 km (OR: 2.15; 95% CI 1.00–4.67). However, they did not find an increased risk of leukemia with shorter distance from the source, a decrease in risk with increasing inverted quadratic distance, or the linear dose–response relationship suggested by Michelozzi et al. (2002). When the analysis

Table 4
Radio frequency electromagnetic fields studies.

Authors	Country, study period, design	Exposure assessment	Exposure category	Outcome [95% CI]
Michelozzi et al. (2002)	Italy (Rome/Vatican)	Measurements of all transmissions (5–600) kW	RF	
	1987–1999	Cumulative areas around the radio station.	Distances (0–2) km	SMR: 6.1 [0.40–27.5]
	Ecologic: 8 cases out		Distances (0–4) km	SMR: 2.9 [0.7–7.6]
	of 49,656 inhabitants		Distances (0–6) km	SMR: 2.2 [1.0–4.1]
			Distances (0–8) km	SMR: 1.5 [0.7–2.7]
			Distances (0–10) km	SMR: 1.2 [0.6–2.3]
Hocking and Gordon (2003)	Australia (Sydney)	Measurements of RF (TV towers): In an inner	AMF	
	Ecologic: 123ALL cases	ring (radius of 4 km) of 3 municipalities	Mortality ratio inner ring	RR: 2.1 [1.1–4.0]
		surrounding TV towers, compared with outer	compared with outer ring.	
		ring (radius between 4–12 km) of 6		
		municipalities surrounding TV towers		
Ha et al. (2007)	South Korea	31 towers of ≥20 kW power, operating 24 h/day	AMF	
	1993–1999		Distance 20 km	
	Case–control: 1928 cases		Distance ≤ 2 km	
	and 3082 controls from		All leukemia	OR: 2.15 [1.00–4.67]
	the national medical		Lymphotic leukemia (continuous)	OR: 1.60 [0.69–3.72]
	insurance data system		Lymphotic leukemia (categorical)	
			Second quartile	OR: 1.39 [1.04–1.86]
			Third quartile	OR: 1.59 [1.19–2.11]
Merzenich et al. (2008)	West Germany	High-power radio and TV broadcast towers, 1	Distances (10–15) km	
	2005–2007	AM and 8 FM/TV transmitters	ALL	
	Case–control: 1959 cases		Distances (0–<2) km	OR: 1.31 [0.80–2.15]
	from the German childhood		Distances (2–6) km	OR: 0.82 [0.66–1.03]
	cancer registry, and 5848 controls		Distances (6–10) km	OR: 0.76 [0.63–0.91]
			AML	
			Distances (0–<2) km	OR: 0.19 [0.02–1.47]
			Distances (2–6) km	OR: 0.75 [0.45–1.24]
			Distances (6–10) km	OR: 1.00 [0.68–1.47]
			(ALL + AML)	
			Distances (0–<2) km	OR: 1.04 [0.65–1.67]
			Distances (2–6) km	OR: 0.81 [0.66–0.99]
			Distances (6–10) km	OR: 0.79 [0.67–0.93]

AMF: frequency modulated amplitude; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; SMR: standardized mortality ratio; RF: radio frequency.

was conducted separately for ALL and acute myeloid leukemia (AML), the total exposure to RF showed only a significant association with ALL ($p = 0.06$) but not with AML. Children were classified according to the exposure received, and those receiving a higher level of exposure had an increased risk of ALL, with an OR of 1.39 (95% CI 1.04–1.86) for the second quartile and of 1.59 (95% CI 1.19–2.11) for the third quartile in comparison to the first quartile.

Between 2005 and 2007, Merzenich et al. performed a case–control study in Germany, including 1959 cases (diagnosed between 1984 and 2003) and 5848 matched controls. The most frequent diagnosis among the cases was ALL (81.0%) (Merzenich et al., 2008). They investigated the distribution of RF (dB [microvolts/m]) from all radio/TV stations a year before diagnosis and the distance between the residence of study subjects and the nearest station. They compared individuals residing ≤2 km distant and at 30 km from a radio/TV station and found that the distance was an important determinant of exposure to RF EMR, with a considerable variation in exposure from 85 dB to >120 dB (microvolts/m) at intermediate distances (20 km). However, the authors found no significant difference in the risk for any type of leukemia as a function of the distance from either AM or FM/TV transmitters.

5. Discussion

Most of the studies reviewed here found an association between exposure to EMR and the risk of childhood leukemia, although statistical significance was not always reached. Taking into account exposure values of ≥0.3 μT, the risk of cancer is significant and greater than 1 in the majority of datasets analyzed in our review (Table 3), despite the wide interval ranges in some of them. In fact, half ($n = 20$) of these datasets show statistically significant increases and none yields a statistically significant decrease. Hence, according to this epidemiological evidence, there is an increased risk of leukemia in children exposed to low electromagnetical fields of ≥0.3 μT. However, the authors that detected an association generally attributed it to confounding factors, potential biases, misclassifications of exposure, or simple chance. For this reason, no definitive conclusions can be drawn at this point in time.

Given the uncertainty on this issue, it seems appropriate to clarify some key aspects of the research to date. Different methods have been used to estimate exposure. Some authors measured exposure indirectly, by using the original wire code method developed by Wertheimer and Leeper (1979) or a modification (Leeper et al., 1991; Savitz and Kaune, 1993). Their results have not significantly differed from those obtained by direct methods, e.g., 24-h spot measurements (Thomas et al., 1999; Angelillo and Villari, 1999).

Numerous researchers have claimed that indirect measurements are susceptible to error and are not valid for the quantification of exposure to NIR (Jones et al., 1993; Savitz and Poole, 2001). Besides, the data used in many of the studies are from registers and censuses or are approximations derived from epidemiological questionnaires that are not always designed to establish the timing and duration of exposure or to collect data on potentially confounding variables (e.g., place of residence, occupation, and living habits). The use of questionnaires often leaves researchers at the mercy of the quality and validity of the questions and faces them with problems of legibility or absence of annotations. These drawbacks limit the possibility of obtaining reliable information and can produce misclassifications of exposure (Delgado Rodríguez and Palma Pérez, 2006). Variability in study populations and in epidemiological design may also contribute to the disparity in results to date (Delgado Rodríguez and Palma Pérez, 2006).

Hence, discrepancies among the conclusions of the studies in this review may also be influenced by confounding factors, selection bias, and misclassification (ICNIRP, 2001; Wartenberg, 2001; Greenland, 2003; Kheifets and Shimkhada, 2005; Kundi, 2007; Kheifets and

Oksuzyan, 2008; Schüz and Ahlbom, 2008). It is difficult to identify confounding factors when knowledge of the etiology of the disease is incomplete, as in the case of childhood leukemia. Speculative hypotheses are usually proposed to explain away observations of an association between exposure to magnetic fields and childhood leukemia (Kheifets and Shimkhada, 2005). The fact that we live in a complex EMR environment with a multiplicity of exposures makes it especially complicated to interpret population studies on EMR. We are now exposed to all types of electrical pollution from various sources and at myriad frequencies, confounding our ability to assess the contribution of a single determinant. This adds to the value of research performed before the current ubiquitous electrical excess.

Misclassification of exposure may mask association with the disease or understate its magnitude (ICNIRP, 2001; Greenland and Kheifets, 2006). However, it is unlikely that only one design flaw has a consistent effect across studies and represents the sole explanation for the alleged association (Wartenberg, 2001; Kheifets and Oksuzyan, 2008; Schüz and Ahlbom, 2008). Selection bias would be another factor to consider in the interpretation of these results. Most of the data suggesting an increased risk of childhood leukemia are usually based on relatively small numbers of exposed children, and some social levels have been underrepresented in the reviewed studies.

Investigations into the damage produced during the first years of life should consider exposure before and during pregnancy. Birth defects can result from genetic or epigenetic damage as well as from effects on the embryo or fetus, and both may be related to environmental exposure of the parent before conception or during the pregnancy (Wu et al., 2007; Cech et al., 2007; Leitgeb and Cech, 2008). It is therefore critical for researchers to define *a priori* the type and “window” of exposure to be assessed. For example, maternal exposure to NIR during organogenesis has been proposed as a cause of defects observed in early life (Feychting et al., 2000; Lee et al., 2002; Li et al., 2002; Infante-Rivard and Deadman, 2003; Pearce et al., 2007). It has also been suggested that exposure of the father may play a role in some congenital defects through epigenetic or genetic damage to germ cells (Jensen et al., 2004).

According to the WHO Experts' Committee of Electromagnetic Fields and Public Health (WHO: www.who.int/emf), between 1% and 4% of children in the world are exposed to magnetic fields above 0.4 µT. Current exposure limits for the general public are based on known thermal effects, in the range of 100 µT range at 50 Hz and higher frequencies (Table 2) (ICNIRP, 1998). Moreover, current safety levels are based on short-term or immediate effects, and cancers and other diseases can have a long latency period. However, the Spanish “Declaration of Alcalá” (2002) called for safety levels to be reviewed in the light of growing evidence of biological effects at lower levels that are not associated with an increase in temperature (Havas, 2002). The majority of the evidence comes from *in vitro* laboratory and animal studies, and is of very limited use for determining health risk (Ruiz-Gomez and Martinez-Morillo, 2009). Nevertheless, epidemiological evidence to date and the severity of the potential harm, especially to children, would argue in favor of application of the precautionary principle. Several reports have recommended use of the precautionary principle for these exposures [Kundi et al., 2009, Herberman, 2008; International Commission for Electromagnetic Safety (ICEMS) 2008; Committee on Non-Ionizing Radiation Protection 2008; Sage et al. 2007]. It is essential to achieve an international standardization of regulatory levels, supporting the adoption of preventive measures to reduce exposures and facilitating comparisons among countries.

Studies to date have not convincingly confirmed or ruled out an association between NIR and the risk of childhood leukemia. Methodological problems to be solved include the proper diagnostic classification of individuals and the estimated exposure to non-ionizing radiation, which may act through various mechanisms of action. There appears to be an urgent need to reconsider exposure limits for low frequency and static magnetic fields, based on sound epidemiological research into the relationship between exposure to NIR and adverse human health effects. In the meantime, it would be advisable to adopt a precautious approach to NIR (RF, MW), limiting body exposure whenever possible and feasible. Further research on the effects of this radiation is required to improve the basis and reliability of the safety standards.

In summary, the epidemiological evidence reviewed in this article reveals a consistent pattern of increased leukemia incidence in children exposed to low electromagnetic fields. This increase is pronounced in children exposed to fields greater than 0.3 µT but can also be observed in weaker fields. However, all of the studies in this area are affected by various confounding variables that make it difficult to conclusively establish a causal relationship at this juncture.

6. Possible future actions

1) Combined laboratory and epidemiological research is warranted to analyze DNA damage in exposed individuals and their offspring as a function of their exposure level, e.g., using COMET or micronucleus assays to study lymphocytes from these populations.

2) It would be useful to establish exposure profiles for different child populations by considering the timing of exposure, particulary during special windows of susceptibility (e.g. pregnancy) region, and the occupational exposure of parents. It would also be of interest to analyze the contribution of different sources to total NIR exposure and to examine differences in exposure for different days of the week, among other variables. Personal exposimeters have been recommended for the estimation of the exposure of populations.

3) It is important to investigate adverse effects to a lower level of exposure than is classically used for risk estimations ($\geq$0.3 µT), comparing between groups with low and high exposure to NIR.

4) It is desirable to consider exposure to electromagnetic fields as a whole, simultaneously measuring electrical and magnetic fields. Most of the studies in the present review solely investigate magnetic fields, which may lead to an underestimation of exposure levels.

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